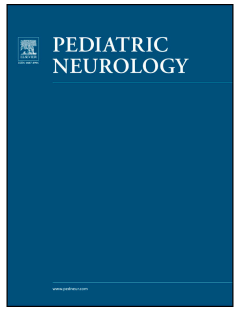

Hand preference develops across childhood and adolescence in extremely preterm children: The EPICure Study

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Hand preference develops across childhood and adolescence in extremely preterm children: The EPICure Study

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What this paper adds:

1. After extremely preterm birth, handedness develops through to 19 years
2. Left/mixed handedness is more common at each age compared to controls
3. Neonatal brain injury is associated with increased left/mixed handedness
4. Cognitive impairment is only weakly associated with left handedness at 19y

Abstract

Aim: To determine how handedness changes with age, and its relation to brain injury and cognition in births before 26 weeks of gestation.

Methods: We used data from the EPICure study of health and development following birth in the British Isles in 1995. Handedness was determined by direct observation during standardised testing at 2.5, 6 and 11 years of age and by self-report using the Edinburgh Handedness Inventory at 19 years. Control data from term births were included at 6, 11 and 19 years.

Results: In extremely preterm children left handedness increased from 9% to 27% between 2.5y and 19y, with a progressive reduction in mixed handedness from 59% to 13%. Although individual handedness scores varied over childhood, the between-group effects were consistent through 19 years, with greatest differences in females. In extremely preterm participants, neonatal brain injury was associated with lower right handedness scores at each age and left-handed participants had lower cognitive scores at 19 years after controlling for confounders, but not at other ages.

Conclusion: Increasing hand lateralisation is seen over childhood in extremely preterm survivors, but consistently more have non-right preferences at each age than controls.

190 words

Hand preference may be easily and reliably assessed by direct examination using standardised presentation of everyday tasks. Around 85-90% of individuals in the general population demonstrate right hand preference. In contrast, studies reporting the laterality of populations of preterm children have frequently demonstrated an excess of non-right-hand preferences, an observation that does not appear to be related to the presence or laterality of observed brain injury[1]. In a recent systematic review, Domellöf and colleagues estimated the odds of preterm children being non-right handed compared to term-born children at 2.12 (95%CI: 1.59; 2.78).[2] They identified that in some, but not all studies there was concordance between non-right handedness and poorer neuropsychological function. Thus, it remains unclear whether this excess represented children with abnormal brain development and impaired performance or whether it was a specific feature of altered laterality in response to preterm birth. More recently in an neurocognitive evaluation of the Extremely Low Gestational Age Newborn (ELGAN) cohort at 10 years of age, left-handed and right-handed children performed similarly but those with mixed handedness had greater odds of functional neurocognitive deficits.[3] Although it is acknowledged that lateral preferences tend to be clear from 3 years of age in the general population, there are no data on the evolution of laterality across childhood in preterm children to contextualise observations of lateral preferences at single ages, or to determine whether associations with neuropsychological functioning are constant at different ages. Such information may inform understanding of the different functional developmental organisation of the brain after preterm birth, compared to typical development following normal gestation.

In the EPICure Study, a longitudinal study of births in the UK and Ireland in 1995 at 25 completed weeks of gestation or less (extreme preterm; EP), we have evaluated survivors through to 19 years of age. At each assessment, hand preferences were established as part of a multidomain assessment either at home (2.5y), school (6y and 11y) or in a central London clinical research facility (19y). In this paper we test three hypotheses: firstly, that hand preferences in the EP population are consistently more non-right compared to controls over the study assessments; secondly that brain injury does not alter the distribution of hand preferences; and thirdly that the excess of non-right preferences among EP children is associated with lower IQ and academic attainment.

Methods

Population: The identification and perinatal outcomes for this cohort have been described previously[4], together with outcomes at 2.5[5], 6[6], and 11 years[7]. At 19 years we performed a centre-based assessment at the Clinical Research Facility at University College Hospital, London[8]. There was significant attrition between 2.5 (n=300) and 19 years (n=129; Figure 1). Term-born classmates of EP children were recruited at 6 (n=160) and 11 years (n=153) and those attending at 11 years were invited to the 19-year assessment (n=65 attendees). Informed consent was obtained from parents up to 11 years and from individual participants at 19 years. Ethical approval was obtained de novo for each follow up assessment. At 19 years approval was given by the South Central Hampshire A Research Ethics Committee (Ref: 13/SC/0514).

Methods: Hand preference was measured by direct observation of 7 tasks as part of the home or school-based assessment. Children were seated at a desk and each task presented in the midline with hands at rest away from the desk surface. The seven tasks comprised: picking up a cube, placing a block on a tower, using a spoon, using a pen, using a crayon, pointing and throwing a ball. If the child used more than one hand for each task the full item set was repeated. Scores were +1 for use of right hand, -1 for left hand and 0 where both hands were used. Scores with the left and right hand were totalled to give a range from 14 (complete right hand preference (RH)) to -14 (complete left hand preference (LH)). At 19 years, individual participants completed the Edinburgh Handedness inventory[9]. From the original 10-item set, three items (using a knife, a broom and opening a box lid) were dropped as suggested by an analysis of internal consistency among items,[10] leaving 7 items that were summed to produce scores from 14 to -14 to match the earlier assessment scores.

Parental hand preference was determined by self-report at the time of the 2.5y assessment on a five-point scale as “always” left/right, “mainly” left/right and “use either hand” for all tasks.

Hand preference in our sample was defined *a priori* following visual inspection of the distribution of control child scores at 11 years (Figure s1), being the age at which controls were most frequently right handed and the latest age of direct observation. We defined groups as RH (+10 to +14) and LH

(-14 to -10). Individuals scoring -9 to +9 were termed mixed handed (MH). These cut offs were applied at each age to provide a consistent definition.

Data from the main study were combined to provide perinatal data, socioeconomic status (grouped as high, medium and low), developmental outcome at 2.5y (Mental Development Index (MDI), Bayley Scales of Infant and Toddler Development 2E, IQ at 6y and 11y (Mental Processing Composite (MPC), Kaufman Assessment Battery for Children (KABC)), academic attainment at 11y (KABC MPC; standardised composite scores in reading and mathematics, Wechsler Individual Achievement Test 2E mathematics and reading composite) and 19y (Full Scale IQ, Wechsler Abbreviated Scale of Intelligence - Second Edition (WASI-II)) and the presence of cerebral palsy (with a Gross Motor Function Classification of $\geq$2 at any age). All outcome methodology has been described previously.[4-7]

Statistical analysis: Mean handedness scores with 95% confidence intervals (CI) in EP participants and term-born controls were calculated at each time point stratified by the group variables.

Multilevel modelling was used to investigate trajectories of handedness scores from infancy to adulthood using Stata 14.2, treating the data as having a hierarchical structure with observations at each time point nested within each individual. This allows adjustment for missing observations where the individual was not assessed. In the analysis comparing EP and control groups, age was fitted as a random effect, which allows both the average level and the change in handedness score over age to vary between individuals. Age was centred at 6 years. A group term was added as a fixed covariate to test for a difference in intercept between the EP and control groups. An interaction term between age and group was then added to test whether the EP and control groups varied by slope, and then a quadratic function of age to test for curvature in the trajectories (Table S1). The likelihood ratio test was used to evaluate the difference and compare the goodness of fit between models.

The effects of participant sex and SES were examined by adding them separately to the model as fixed covariates and then as interactions with group (Table S2). For a parameter to be retained in the model, it was required to have a ‘p’ value <0.05 in the likelihood ratio test. Analyses were first conducted in all participants with data available at any time point, and then restricted to those with complete longitudinal data only.

Multinomial logistic regression models were used to estimate relative risk ratios (RRRs) of left-handed preference (LH) and mixed-handed preference (MH) to right-handed preference (RH, the reference group) for EP participants at all ages. We then adjusted for participant sex in the models. Similar analyses were conducted within the EP group to test the effect of neonatal brain injury and parental handedness on handedness scores, with further adjustments for sex and gestational age. The risk for EP participants (controls as reference) was reported as relative risk ratios (RRRs) with 95% confidence intervals. Multiple linear regression models were used to analyse the effect of hand preference scores on cognitive score, reading and maths attainment in EP participants and controls, respectively. We adjusted for neonatal brain injury, gestational age and sex for EP participants, and sex for controls. Mean score differences between participants with LH/MH and RH and their 95% confidence intervals were reported.

Results

The EPICure cohort was evaluated at 4 ages. Progressive loss to follow up occurred over the course of 19 years such that we retained 129 of the original 315 discharges or 42% of 306 long term survivors at 19 years (Figure 1). Similar attrition occurred in the control population; 42% of those assessed at 11 years were also assessed at 19 years. A full drop out analysis has been published.[7]

In previous studies parental handedness has been shown to affect the development of hand preference. At 2.5 years, 89% of mothers of EP infants (n=240) and 87% of fathers (n=206) reported themselves to be RH, which is the expected population frequency. Only one mother reported that she was uncertain. We also asked parents to estimate their child's hand preference on the same scale. There was relatively poor agreement between this and our standardised observation (agreement: 44%; Kappa: 0.227; p<.001; Table s6).

Changes in hand preferences over time: Hand preference was evaluated in all directly evaluated participants. Among the populations evaluated at each age, the distributions of hand preferences categorised into three groups (RH, MH, LH) changed between 6 and 19 years among EP participants and controls (Table 1). A similar pattern was observed whether all participants evaluated at each age, only those seen at each age point or only participants without cerebral palsy were analysed (Figure s2). Compared to controls, among the EP group greater proportions with both mixed and LH preferences were seen at each age. At 2.5 years the majority of EP participants had MH (55%): only 32% were RH and 10% LH, as defined. Compared to controls, from 6 to 19 years EP participants were more likely to be left handed (at 6 years RRR: 7.2 (2.9-17.7); at 11y: 4.2 (2.0-8.8); at 19y: 4.2 (1.5-11.6)) and MH reduced in frequency (Table 1).

Centred on classification of preferences at 11 years, changes in hand preference scores over the study period are shown in Figure 2 and Table s3. In the EP group at 2.5 years and in both groups at 6 years the spread of scores was broader than at 11 years indicating inconsistency in individuals. Self-assessment at 19 years produced a similarly broader range of scores.

Multilevel modelling of handedness scores was used to account for loss to follow up (Table s2 & s4). Handedness scores tended to rise in all models to 11 years (Fig 3a). Differences in mean scores between the EP and control groups remained similar between 6 and 19 years in all participants. When grouped by sex, differences in scores were greatest among females (Fig 3b). Maternal (Fig 3d) and paternal hand preference (not shown) did not affect EP handedness scores.

Effect of brain injury: Compared with EP participants with no brain injury on ultrasound or subependymal haemorrhage only, more severe neonatal brain injury was positively associated with a higher occurrence of LH and MH in EP participants at all ages except for 19 years (Table s5; LH: Relative risk ratio (RRR) ranging from 2.9 to 4.2; MH: RRR ranging 2.3 to 2.6); these associations persisted after adjusting for sex and gestational age In the model, handedness scores of EP participants with moderate/severe neonatal brain injury were on average 3.8 points below participants with no/mild brain injury (95% CI -6.1 to -1.4, P=0.002). (Fig 3c).

Association of hand preference with cognitive scores: IQ and academic attainment were significantly higher in controls compared to EP participants, as described previously.[6] Among the EP group, scores tended to be higher in right compared to left or mixed handed groups (table 2). Significant differences from right handed participants were only found among left handed participants in IQ and reading at 11 years and in IQ at 19 years, but after adjustment for neonatal brain injury, sex and gestational age only the IQ differences at 19 years persisted (adjusted difference in means: -6.8 points (95% confidence interval: -13.2, -0.3)).

Discussion

Extremely preterm survivors more frequently have non-right preferences compared to controls. Using multilevel modelling to evaluate the changes over time, we demonstrated that the differences in handedness scores between EP and term-born controls persisted over 19 years. Among the EP group, handedness became progressively more polarised with age, and MH became less frequent. Assessments showed variability in observed handedness particularly among EP individuals, with less variation in controls. EP participants who had evidence of intraventricular haemorrhage or periventricular leukomalacia were more likely to be non-right handed even after adjustment for important confounding variables, namely sex and gestational age. The relationship between the excess of LH and MH in the EP group with lower neurocognitive scores appeared to be weak during childhood. It is notable that in our study after adjustment for confounders, IQ scores were significantly reduced by approximately 0.4 standard deviations only at 19 years in LH participants.

The trajectory of handedness has not been studied before in preterm populations, and indeed few studies have attempted to carry out direct observations of hand preference. It is commonly held that lateral preferences become apparent in the third year. At 2.5 years, when we might have expected preferences to be becoming clear, only 32% of EP children were RH and over half were mixed. Our data further suggest that, following extremely immature birth, these preferences are inconsistent over childhood, as shown in Figure 2, and the measures made at 6 and 11 years still demonstrate transition to more established preferences at 19 years – 30% of those tested showed MH at 6, reducing to 21% at 11 years and 13% at 19 years. In contrast, LH increases in prevalence over the age range. The distribution of scores in the control group was closer to that expected in the general population. We used multilevel modelling to study the evolution of preferences over the four observations. Both extremely preterm and control groups showed similar trends to increasing right lateralisation but change was greater in the EP group (Figure s1).

Most other studies have assessed handedness using parental questionnaires or accepting the preferred hand for writing. We were disappointed at the low agreement between handedness scores and parent report, which showed poor concurrent agreement at 2.5 years of age (kappa 0.227). Of interest, using parent assessment at the first visit, the 11 year classification shows slightly better agreement (67.5%; kappa 0.412; Table s6). It is a moot point as to which may be the more accurate reflection of "true" handedness. Our observations were conducted in a standardised fashion with identical presentation of tasks in the midline with both hands placed on the table. In contrast, parent report reflects accumulated observation, which may reflect bias in the presentation of tasks to one particular hand by the parent. Hence, we report direct standardised observation.

The relationship between handedness and measures of neurocognitive performance appear inconsistent across the literature.[2] We hypothesised that this excess of non-RHP among EP participants might be associated with poorer cognitive and education scores as has been shown in some other studies, but were only able to demonstrate differences at 11 and 19 years and only among those who were LH rather than MH; moreover only the 19 year findings correlated with measured IQ after adjustment for prespecified confounders and multiple comparisons. At 19 years attrition was highest making this observation least reliable, although our modelling suggests that both hand preference distribution and cognitive scores remain stable. Interestingly, the magnitude of the difference in means was similar for controls at 19 years, although not of statistical significance possibly because of the smaller sample size. This contrasts with the findings from the ELGAN study where a range of lower scores appeared to be associated with mixed hand preference, using parent-assigned hand preference.[3]

The strengths of our study lie in the longitudinal nature of the assessments and standardised testing undertaken during childhood. We used direct observation during a specific standardised test to classify hand preference in childhood and a well-validated self-completion questionnaire at 19 years. We reduced the number of variables used in our assessment in keeping with recommendations to provide a consistent scoring system in line with our direct observations. We suggest that direct measures may be more reliable than parent report, as used in other studies. In our study, we describe only poor to mild agreement between parent report and direct observation at 2.5 years.

We used multilevel modelling to adjust for attrition during follow up and adjusted for variables that *a priori* might confound any relationship. For example, key factors associated with cognitive scores in previous studies were male sex, lower gestation at birth, and evidence of brain injury. Likewise, males may show stronger right dominance than females in the general population. We further used continuous dimensional measures of handedness, to minimise the assumptions made during classification of hand preference. We chose a single measure of cognitive function at each age to avoid problems from multiple testing of related subscales, and included standardised educational measures of mathematics and reading, which have been consistently shown to detect poorer performance in preterm populations.

The major weakness is the high level of attrition. However, the population that were not examined at 19 years showed few differences on a range of perinatal variables and similar frequencies of hand preferences were seen in the smaller cohort evaluated at each time point, when compared to the full population examined at each age. Nonetheless small differences might have biased these findings. We also chose to use the Edinburgh Handedness Inventory at 19 years because of time pressures within the face-to-face centre-based evaluation schedule. Finally, there are no accepted formal definitions of laterality on testing. We chose cut points after inspection of control participant data at 11 years, the latest age at which we directly observed preferences, and applied it equally to define right and left handedness at each age for this study. Despite our *a priori* definition, it is possible that a different cut point may have altered the findings.

We have confirmed the excess of non-right-hand preferences in a population of extremely preterm children through to young adult life. In our population we demonstrate the progression of lateralisation over 19 years. Expected associations with cognitive test results were generally not found and restricted to those with left hand preference; the significance and import of this observation remain obscure. Non-right laterality appears to be a relatively weak indicator of neurodevelopmental problems in the EP population.

Well established handedness may reflect focused organisation of the central nervous system. MRI studies suggest that the preterm brain is organised in a less focused fashion compared to the term brain, with wider activation during fMRI tasks[11] and differences in conectivity.[12] The poor lateralisation of hand preference in this extremely preterm cohort may reflect this and provide explanation for this consistent finding.

3102 words

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Legends for figures

Figure 1: Disposition of the EPICure cohort and controls through 19 years of age

Figure 2: Change in individual hand preference scores in extremely preterm and control participants based on predominant hand preference observed at 11 years for individuals seen at each age. Higher scores indicate greater right hand preference.

Figure 3: Multilevel modelling results (random slope model) for hand preference scores from 2.5 years through 19 years in extremely preterm children and controls.

Table 1: Distribution of hand preferences among extremely preterm children and controls at each assessment point.

		Extremely preterm				Controls			Relative risk ratio (95%CI) *	
Cross-sectional analysis: all participants with at least one assessment										
Age	**n**	**Right handed (score ≥10)**	**Mixed handed (score +9,-9)**	**Left Handed (score ≤-10)**	**n**	**Right handed (score ≥10)**	**Mixed handed (score +9,-9)**	**Left Handed (score ≤-10)**	**Mixed handed**	**Left handed**
2.5y	277	89 (32.1%)	162 (58.5%)	26 (9.4%)		-	-	-	-	-
6y	206	107 (51.9%)	62 (30.1%)	37 (18.0%)	159	125 (78.6%)	28 (17.6%)	6 (3.8%)	2.6 (1.5, 4.3)	7.2 (2.9, 17.7)
11y	210	131 (62.4%)	36 (17.1%)	43 (20.5%)	152	129 (84.9%)	13 (8.5%)	10 (6.6%)	2.7 (1.4, 5.4)	4.2 (2.0, 8.8)
19y	115	69 (60.0%)	15 (13.0%)	31 (27.0%)	62	47 (75.8%)	10 (16.1%)	5 (8.1%)	1.0 (0.4, 2.5)	4.2 (1.5, 11.6)
Longitudinal analysis: participants with all assessments excluding those with CP										
		Extremely Preterm				**Controls**				
2.5y	91	29 (31.9%)	50 (55.0%)	12 (13.2%)		-	-	-	-	-
6y	91	39 (44.3%)	34 (38.6%)	15 (17.1%)	54	42 (77.8%)	10 (18.5%)	2 (3.7%)	3.7 (1.6, 8.4)	8.1 (1.7, 37.6,)
11y	91	54 (59.3%)	19 (20.9%)	18 (19.8%)	54	43 (79.6%)	8 (14.8%)	3 (5.6%)	1.9 (0.8, 4.7)	4.8 (1.3, 17.3)
19y	91	51 (58.6%)	12 (13.8%)	24 (27.6%)	54	40 (78.4%)	6 (11.8%)	5 (9.8%)	1.6 (0.6, 4.6)	3.8 (1.3, 11.0)

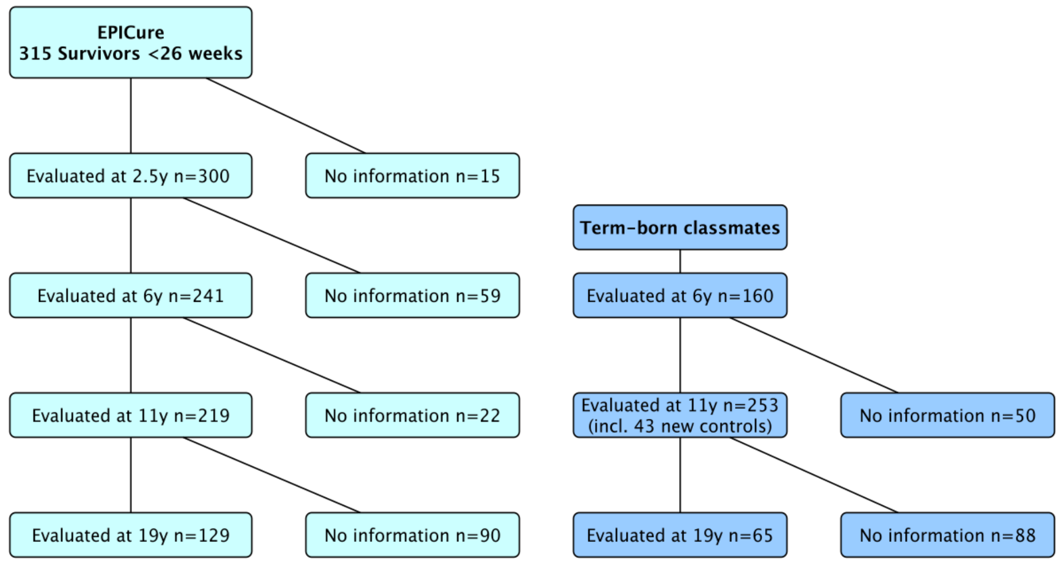
** multinomial logistic regression; reference category: right-handedness*

Table 2: Hand preferences and cognitive/attainment scores for extremely preterm and control participants (significant differences in means shown in bold)

		Cognitive scores			Unadjusted		Adjusted [+]	
			Mean (SD)		Difference in means from RH (95% CI)		Difference in means from RH (95% CI)	
Age	**Test**	**Right handed**	**Mixed handed**	**Left handed**	**Mixed handed**	**Left handed**	**Mixed handed**	**Left Handed**
Extremely Preterm participants								
2.5y	BSID2	82.3 (14.0)	81.4 (14.7)	80.9 (14.4)	-0.9 (-4.8, 3.0)	-1.5 (-8.3, 5.3)	0.6 (-3.3, 4.4)	-0.9 (-7.6, 5.7)
6y	KABC	89.3 (13.0)	86.5 (14.1)	84.5 (13.8)	-2.9 (-7.1, 1.3)	-4.9 (-10.0, 0.2)	-1.8 (-5.9, 2.2)	-4.4 (-9.2, 0.5)
11y	KABC	87.4 (14.4)	84.3 (16.4)	81.4 (18.4)	-3.0 (-9.0, 2.8)	**-6.0 (-11.4, -0.5)**	-1.7 (-7.4, 4.0)	-4.6 (-10.0, 0.7)
	Reading	84.3 (17.9)	80.2 (19.6)	76.6 (19.7)	-4.0 (-11.2, 3.1)	**-7.7 (-14.1, -1.2)**	-2.7 (-9.8, 4.4)	-6.1 (-12.7, 0.4)
	Mathematics	74.4 (19.1)	71.2 (21.6)	68.1 (21.9)	-3.2 (-10.8, 4.5)	-6.3 (-13.3, 0.7)	-1.7 (-9.3, 5.9)	-4.2 (-11.3, 2.9)
19y	WASI-II	89.6 (14.6)	90.1 (16.1)	82.9 (14.0)	0.6 (-7.7, 8.9)	**-6.6 (-12.9, -0.3)**	0.5 (-7.9, 8.9)	**-6.8 (-13.2, -0.3)**
Control participants								
6y	KABC	106.0 (11.9)	106.1 (11.8)	100.7 (9.0)	0.1 (-4.8, 4.9)	-5.3 (-15.1, 4.4)	0.0 (-4.9, 4.9)	-5.5 (-15.3, 4.4)
11y	KABC	104.0 (11.0)	103.8 (13.9)	106.0 (9.7)	-0.2 (-6.6, 6.2)	2.0 (-5.2, 9.3)	-0.1 (-6.6, 6.3)	2.1 (-5.2, 9.4)
19y	WASI-II	104.0 (10.0)	103.1 (6.6)	111.0 (14.6)	-0.9 (-7.8, 6.1)	7.0 (-2.4, 16.5)	-1.1 (-8.2, 6.0)	6.6 (-3.0, 16.2)

[+]*: EP group adjusted for neonatal brain injury, sex and gestational age; control group adjusted for sex; multiple linear regression analysis*

Figure 1


EPICure
315 Survivors <26 weeks
Evaluated at 2.5y n=300
No information n=15
Evaluated at 6y n=241
No information n=59
Evaluated at 11y n=219
No information n=22
Evaluated at 19y n=129
No information n=90
Term-born classmates
Evaluated at 6y n=160
Evaluated at 11y n=253
(incl. 43 new controls)
No information n=50
Evaluated at 19y n=65
No information n=88

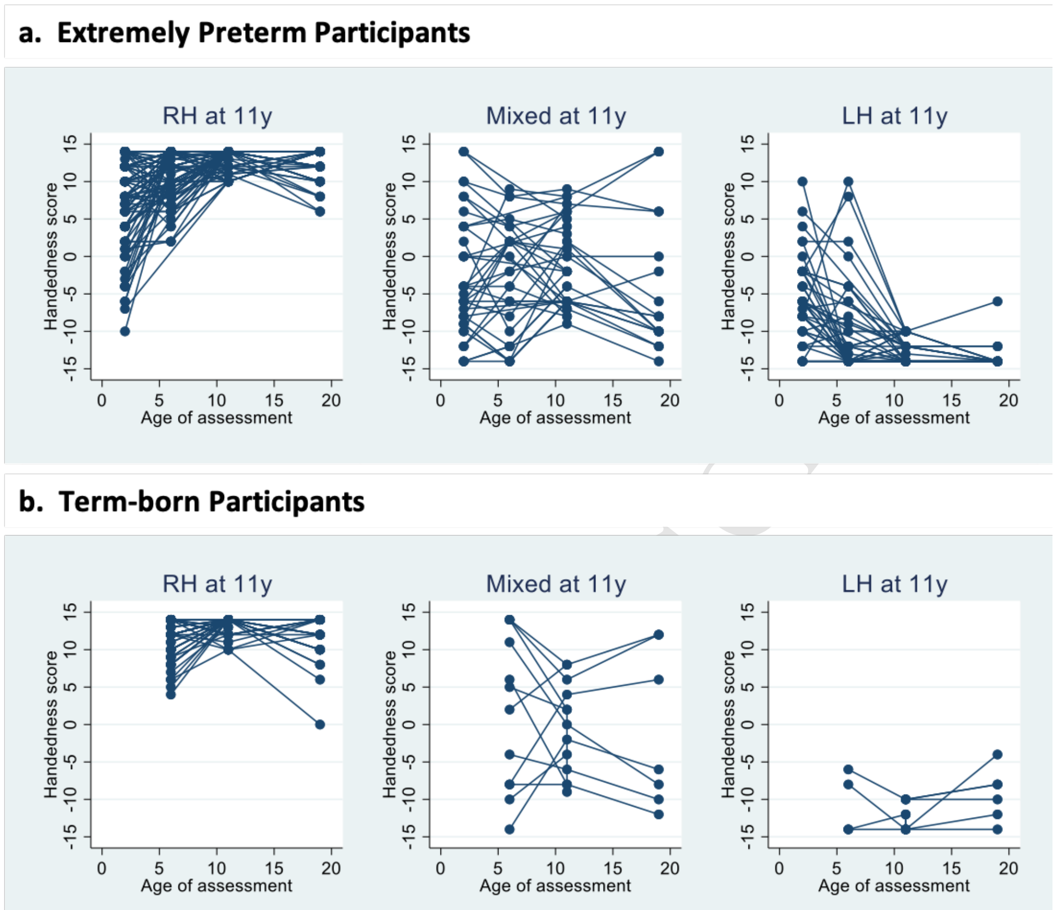

a. Extremely Preterm Participants
RH at 11y
Mixed at 11y
LH at 11y
Handedness score
Age of assessment
-15
-10
-5
0
5
10
15
20
b. Term-born Participants

Figure 2

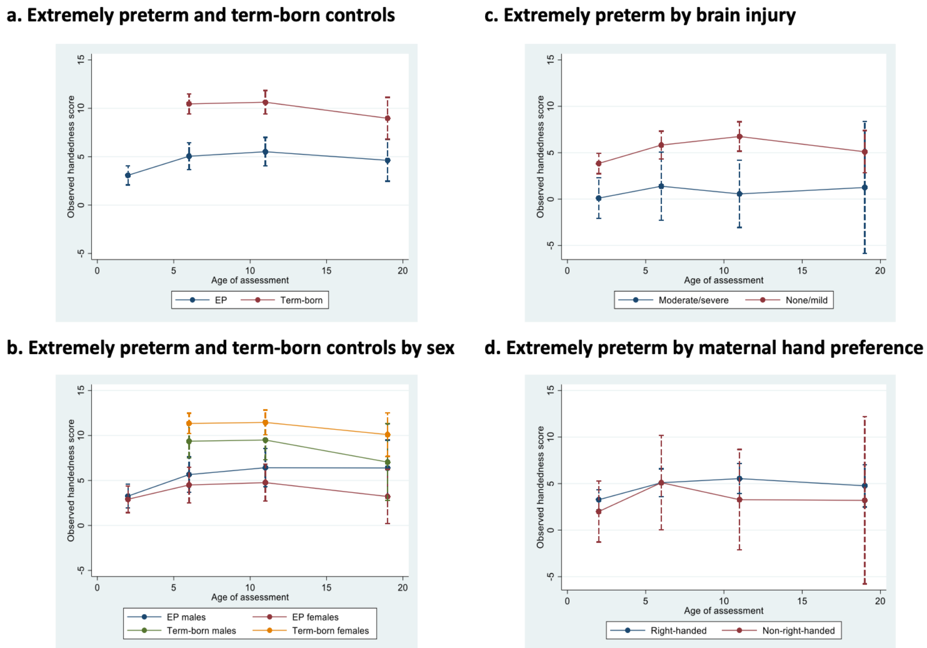

a. Extremely preterm and term-born controls
c. Extremely preterm by brain injury
b. Extremely preterm and term-born controls by sex
d. Extremely preterm by maternal hand preference
Observed handedness score
Age of assessment
EP
Term-born
Moderate/severe
None/mild
EP males
EP females
Term-born males
Term-born females
Right-handed
Non-right-handed

Figure 3